PSJ3
Exhibit 170

IWG Submission to FDA Docket

INTRODUCTION

On February 6, 2009 and again on March 3, 2009, the Food and Drug Administration (FDA) requested that industry manufacturers assist the agency in developing a single REMS for long acting and extended-release opioid drugs formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. The Industry Working Group (IWG) was formed in response to that request.

During the FDA Public Meeting held on May 27 and 28, 2009, a presentation was given by the IWG and included an overview of the Industry Working Group, who we are and what we have achieved to date, specifics of the IWG class-wide REMS and the IWG's next steps and the activities required to complete this important initiative. At the conclusion of the presentation, FDA asked 8 specific questions to IWG and requested that responses be submitted to the docket. The pharmaceutical companies that make up the Industry Working Group (IWG) have addressed these questions in the following document.

All pharmaceutical companies that make up the IWG (Appendix A) are committed to working with the FDA in the development of a class-wide REMS for extended-release opioids and methadone. The therapeutic value of extended-release and long-acting analgesics is well-documented (Coluzzi & Mattia, 2005; Amabile & Bowman, 2006; Matsumoto, 2007). These medicines, however, also carry known risks of overdose and abuse (Cicero et al., 2005; Manchikanti & Singh, 2008).

The IWG views the development of a feasible and functional class-wide REMS as a collaborative process. The IWG therefore anticipates productive dialogue with the FDA and other stakeholders to achieve our mutual goals of reducing the risks associated with the products covered by the class-wide REMS while maintaining patient access to these medications.

Whereas individual companies will communicate risks associated with the use of specific products, the class-wide REMS will promulgate important information common to all drugs within the class (e.g., proper patient selection, safe storage conditions, proper disposal, etc). Such information will represent a foundation of risk mitigation upon which product-specific risks are introduced. An effective class-wide REMS must reduce the risks associated with the medication without compromising legitimate patient access to treatment. As such, the IWG recognizes and appreciates the provisions within FDAAA that any REMS should address specific risks without placing undue burdens on patients or the healthcare delivery system(Public Law 110–85, SEPT. 27, 2007 121 STAT. 927).

Healthcare delivery system changes that are intended to control access must be carefully evaluated for the potential unintended impact on those who are already vulnerable to healthcare disparities. Examples of vulnerable populations include patients arising from segments of the elderly, ethnic minorities, those living in poverty, recent immigrants, those living in medically underserved regions and those individuals who do not speak and/or read English well. These and many others already experience difficulty in accessing appropriate healthcare.

The unprecedented scope of a class-wide REMS for opioid analgesics requires a carefully crafted design and implementation that would place the least burden on all stakeholders. The IWG believes that minimizing the burden on healthcare prescribers, dispensers, and patients is critical for enhancing their compliance with programmatic risk management requirements and ultimately improving program efficacy.

The IWG looks forward to working closely with FDA and other stakeholders to create a REMS appropriate for the class – a REMS that is successful in achieving its underlying objective of ensuring that the benefits of extended-release opioids and methadone continue to outweigh the risks associated with: (1) use of high doses of extended release opioids and methadone in non-opioid tolerant and inappropriately selected individuals; (2) abuse; (3) misuse; and (4) overdose, both accidental and intentional while simultaneously preserving access to these medications by patients and not placing undue burden on the healthcare delivery system.

1. IMMEDIATE ACTION vs. GETTING IT RIGHT

What immediate actions can be achieved while working through the long-term plan?

IWG proposes a phased in approach with a timeline that allows for developing, testing, refining, and communicating the individual components of the plan while demonstrating our commitment to the task at hand. This process is presented in three phases: Immediate Actions, Intermediate Steps, and Long-Term Planning.

Immediate Actions

- IWG, in collaboration with FDA, develop and immediately adopt and implement, in conjunction with prescribers, and a Patient Medication Information Sheet that will be distributed to all patients by the prescriber or the designated office staff at the time of prescribing.
- IWG, in collaboration with FDA, develop and distribute to prescribers a standard and consistent Prescriber-Patient Agreement (PPA) that is understandable and can be developed at a level of comprehension that is understood by most or all patients.
- IWG, in collaboration with FDA and DEA, would like to propose the feasibility of credentialing through the DEA registration process for prescribers.
- Standardize the medication guides for all extended-release opioids and methadone
- Working groups will be established immediately to bring all stakeholders together to develop educational programs, including curriculum development, certification, and timelines for implementation.
- Working groups will be established immediately to involve all stakeholders in the development of metrics and establishment of data collection methodologies that are transparent and meaningful in the data recorded.
- Develop a comprehensive communication plan that includes consistent messaging, to raise awareness of all IWG and stakeholder activities using multiple delivery methods, directed at multiple audiences that will include but are not exclusive to: prescribers, dispensers, patients and caregivers regarding safe storage and disposal of opioids to reduce the risks contemplated in the class-wide REMS.

- IWG in collaboration with FDA develop, evaluate and circulate educational tools for prescribers, dispensers and patients that can be utilized on an immediate basis as other tools are developed.

Intermediate Steps

- Continuous monitoring to refine or redefine metrics and action plan.
- Investigate a process for certification of prescribers and dispensers.
- Investigate the possibility of expanding current state prescription monitoring programs to a nationwide program.
- Consistently evaluate established metrics and data collected to examine impact of immediate actions on reducing the risks contemplated in the class-wide REMS.
- Third-party organizations will be evaluated for implementation of the class-wide REMS.

Long-Term Plan

- Finalize and implement a class-wide REMS for extended-release opioids and methadone, with modifications as indicated by ongoing efforts.
- Ongoing evaluation of established metrics and data collected to examine the impact of immediate and intermediate actions to reduce the risks contemplated in the class-wide REMS.

2. PRESCRIBER-PATIENT AGREEMENT (PPA)

How did the IWG come to support the use of this tool? Some speakers on May 27th were not in support of its use.

The PPA is a tool for communicating important safety information to patients and their caregivers. The IWG believes it is the responsibility of the prescriber or designated staff to facilitate, educate, and communicate with patients and caregivers about the risks of extended-release opioids and methadone. The PPA has become more widespread in its use in the past few years. Many clinicians have become familiar with its use and favor the continuation of this process, and consensus of relevant organizations, such as the American Academy of Pain Medicine and the Federation of State Medical Boards, that recommend the use of such agreements.

Strategic tool:

- Involving two key stakeholders: Prescribers and Patients.
- Addresses proper use, dosing, administration, storage and disposal.
- Clearly communicates the risks entailed from misuse, abuse, diversion, and overdose.
- Establishes the relationship between prescriber and patient, sets boundaries around that relationship, and provides documentation for the patient health record.

PPAs provide a standardized approach:

- The information communicated is standardized and used by all prescribers for all extended-release opioids and methadone.
- Defines roles and responsibilities of the patient and prescriber in the management of chronic pain.

- Establishes boundaries around the use of opioids within the prescriber-patient relationship.

Standard and consistent information distributed to all patients at the time of prescribing:

- Standardized patient educational materials would clearly communicate the risks entailed from misuse, abuse, diversion, overdose and death associated with extended-release opioids and methadone. These materials would also contain pertinent information regarding safe storage and disposal.

PPAs will facilitate a standardized approach with an immediate check and periodic reinforcement of the patient's understanding of critical information. The PPA, when worded properly, used appropriately and consistently, can facilitate education of and communication with patients/caregivers..

3. DEA OR STATE LICENSURE CLARIFICATION

Panel was unclear as to whether it is the DEA registration system or state licensure process that would be utilized to ensure required education; the Panel understood the statements to be in conflict. Clarify and explain how the IWG came to choose this.

There are two distinct groups that need to be addressed in this area: Prescribers and Dispenser. It is important to note that while Prescribers hold DEA licensure, Dispensers (Pharmacists) do not hold individual DEA licenses. Pharmacies register with the DEA to obtain a DEA number in order to dispense controlled substances.

PRESCRIBERS

The IWG supports the use of the DEA registration system as the verification tool for prescriber education because all prescribers of controlled substances need to have a current DEA registration in order to lawfully prescribe. An existing pre-requisite for DEA registration is a current, valid and unrestricted State license to practice a health care profession. The IWG's recommendations are that:

- An accredited third party (or parties) will create the non-product-specific opioid REMS-related certified Continuing Education (CE) program(s) and, if it is decided to do so, certify the prescribers,
- The status of certified prescribers will continually update and DEA will have real-time web-based access allowing confirmation of certification status,
- Analogous to the Drug Addiction Treatment Act of 2000 (DATA 2000) for buprenorphine-prescribing privileges in the treatment of opioid addiction, the process for obtaining an initial or renewal DEA registration to prescribe "narcotic drugs" (as defined in 21 USC 802 (17)) would include verifying that a prescriber is currently certified as one of the prerequisites for registration, and
- The curriculum for DEA registration renewal to prescribe narcotic drugs should be less burdensome than the curriculum required for initial registration and should reinforce principles of safe opioid prescribing, including appropriate patient selection, dosing, administration, safe storage and proper disposal and focus on any new information.

The advantages of using this approach

- It uses a pre-existing system, rather than creating an entirely new one.
- Some prescribers and DEA already have experience with a system similar to what is proposed and have had the opportunity to work out problems.
- This proposal will guarantee that every prescriber of the class of interest has the requisite education/certification.
- Systems that rely on the pharmaceutical industry for communication with prescribers will not reach all prescribers and may in fact only cover a minority of those prescribing drug products in the class.
- Such certification could be expanded easily to include other controlled substances.

DISPENSERS

- An accredited third party (or parties) will create the non-product-specific opioid REMS-related certified Continuing Education (CE) program(s) and, if REMS includes certification as an element of requirement, certify the Dispenser.
- An accredited third party (or parties) will administer and support the opioid REMS-related education for Dispensers as part of the required CE credits for license renewal.

The advantages of using this approach

- It uses a pre-existing system, rather than creating an entirely new one.
- This proposal will guarantee that every dispenser will have the required education that can be certified and verified through valid licensure.

4. METRICS

How does the IWG propose to assess the metrics including, misuse, abuse and patient access?

The most significant aspect of a REMS is the ability to measure whether or not it is effective in meeting its goals. To date, the existing REMS address a single risk associated with a single active pharmaceutical ingredient in the patients who are prescribed the medication. This makes the measurement of outcomes relatively straight forward. The class-wide REMS for extended-release opioids and methadone will be far more complex requiring the measurement of multiple factors, not only in patients who have been prescribed the medication, but in non-patients who obtain the medication from various sources. In order to meet this complex task the IWG must determine the metrics that need to be assessed and the data sources that potentially can be used to measure these outcomes.

The IWG has created a draft list of proposed items to be measured and potential sources of the data (Appendix B). We do not believe this list is exhaustive, but is the beginning of an ongoing process of analyzing what data sources can inform the class-wide REMS with regard to effectiveness and also with regard to unintended consequences. It is not yet clear if the data sources can actually measure the changes necessary to determine whether the class-wide REMS is effective or not. In addition, it will be essential to establish if the data sources are sensitive enough to actually measure the effects, and specific enough to measure significant change.

The metrics table is divided into eight sections indicating the major areas that need to be addressed and the subheadings under each of these sections demonstrate the complexity of this

task. Not only are the number of metrics to be measured large and varied, but many of them need to be defined with terms that are acceptable to all stakeholders, e.g. misuse. Of critical importance, there is no universal agreement of what will indicate success of the class-wide REMS using these or other metrics. If there is a reduction in one metric and a rise in another, will that be considered a positive outcome? For example, if abuse of extended-release opioids and methadone goes down, but patients are not able to obtain needed medications, will that be considered success? Will a decrease in prescription opioid abuse, but a rise in illicit opioid abuse be considered a success? These and other issues will have to be decided prior to the implementation of the class-wide REMS.

Implementing this complex class-wide REMS all at once will make it difficult, if not impossible, to determine which of the numerous aspects of the class-wide REMS are responsible for both the positive and negative outcomes. The most effective way to approach this problem may be to phase in the various components of the class-wide REMS so that each can be carefully measured for its effect.

The IWG has made this start in the measurement process and will continue to refine the metrics table to not only add new elements to measure and the methods to measure them, but to also begin to define what changes in each metric will constitute an effective outcome for the class-wide REMS. This process will require continued refinement in an iterative process with the FDA and all of the many stakeholders.

5. LIMITED INDUSTRY REACH

The IWG mentioned that industry reach is limited. Panel asked for clarification on why reach is limited and what does this mean?

Broad participation with the class-wide REMS from all stakeholders is essential for meeting the underlying objective to reduce the risks contemplated in the class-wide REMS, while preserving access to patients who require these medications for the treatment of their pain. Since the subset of prescribers called upon by sales representatives from companies within the IWG is limited to an unknown fraction of DEA-registrants, industry's ability or "reach" in providing class-wide REMS-related materials/instruction to the full complement of prescribers is, by definition, limited.

In addition to physician prescribers, there are many types of healthcare professionals who may have prescriptive privileges in their State of practice, but are not called upon at all, or only infrequently. Examples include Advanced Registered Nurse Practitioners (ARNPs), dentists (including those who are orofacial pain specialists), Physician's Assistants (PAs), veterinarians, podiatrists, homeopathic practitioners, naturopathic practitioners, and medical psychologists. However, every health care practitioner with State prescriptive authority for controlled substances must also be registered with DEA which, by law and regulation, has 100% reach to prescribers of controlled substances.

While the IWG believes it necessary and appropriate to support education and more thorough patient counseling, the limited reach of the industry and other factors restrict its ability to enforce certain elements of a class-wide REMs. Specifically, the Industry cannot:

- Act as an enforcement arm of the U.S. Government.
- Mandate education for all Health Care Practitioners (HCPs) or patients.
- Control populations which are outside the prescriber-patient relationship (those who seek to abuse extended-release opioids and methadone), and even within the prescriber-patient relationship, the Industry can only recommend controls such as increased education and screening.

Despite these limitations, the IWG believes that Industry can implement the following changes:

- Standardize Medication Guides to make them more understandable.
- Provide Patient Medication Information Sheets and other educational tools which may be more easily understood by the majority of patients.
- Provide and encourage a communication plan for all prescribes and dispensers, as well as a national educational campaign for patients and caregivers throughout the general population. The specific educational offerings and event scheduling would be designed and initiated by professional societies and pain organizations.

To develop a single REMS for extended release opioids and methadone, input and collaboration are needed from a number of organizations and agencies. The IWG needs FDA, DEA, other government agencies and stakeholder support to this initiative.

6. PILOT PROGRAM

How would the IWG propose doing a Pilot program: where would this be done, what would the set-up be, and how would this be looked at?

The IWG is not recommending a "pilot" but rather a phased in approach that allows for developing, testing, refining, and communicating the individual components of a class-wide REMS for extended-release opioids and methadone.

The IWG strongly believes that there must be balance in initiating any phased in program. The objective of the phased in program would be to measure the effectiveness before it is implemented on a nationwide basis. One of the outcomes that could be targeted would be to reduce harm and deaths related to opioid misuse and abuse, but at the same time maintain patients' access to pain treatment.

Set-up:

- A phased in program would include testing of all educational materials, Medication Guide, Prescriber-Patient Agreement, and Patient Medication Information Sheet for comprehension, usefulness, and readability.
- A phased in program could be implemented in multiple ways; the details would need to be determined after input is received from the FDA and various stakeholders.
- Reasonable time frame for implementation of a phased in program and ongoing assessment.
- The phased in program would be implemented and managed by a third party.
- Increase communication among key players and further define roles:

- FDA
- DEA
- State medical and licensing boards
- State and local law enforcement agencies.
- Prescription monitoring programs
- Prescribers: professional societies and regulatory bodies
- Dispensers: professional societies and regulatory bodies
- Patients groups and advocacy groups
- Pharmaceutical industry

Measurement:

- Continuous monitoring to refine or redefine metrics and action plan.
- Generate and evaluate data.
- Develop and test elements of the class-wide REMS and refine processes.
- Communicate and promote acceptance and participation for all stakeholders.

Outcome Measures

- Maintain patient access to pain treatment with extended-release opioids and methadone.
- Reduce the risks contemplated in the class-wide REMS.
- Streamline and standardize processes and communication.
- Finalize the class-wide REMS for extended-release opioids and methadone.
- Collaboration among key players
  - FDA
  - DEA
  - State medical and licensing boards
  - State and local law enforcement agencies
  - Prescription monitoring programs
  - Prescribers: professional societies and regulatory bodies
  - Dispensers: professional societies and regulatory bodies
  - Patient groups and advocacy groups
  - Pharmaceutical industry

At present, there are a large number of groups/organizations from which various elements of the class-wide REMS could be collected and utilized, therefore eliminating the need for creating an entirely new program. The IWG promotes assessing existing programs to facilitate the initiation of a phased in program. This will be cost effective, time sensitive, and allow for flexibility and ongoing evaluation.

7. IMMEDIATE ACTION

The IWG was requested to assess the suggestions of a moratorium and compassionate use program.

Chronic pain has been determined to be a major public health concern, and millions of patients are currently being effectively treated with extended-release opioids and methadone. Restricting these medications or implementing a compassionate use program will likely shift the risks contemplated in the class-wide REMS to other products or to illicit drugs.

There are no regulations recognizing a "compassionate-use" program. Rather, these programs fall under various designations including single patient INDs or formal clinical trials. In each instance, there is a substantial burden on the treating physician and patient to document need, leading inevitably to legitimate patients either being denied access or lengthening the time to receiving adequate pain medication.

A moratorium of any sort denying legitimate pain patients access to effective treatment would create additional pain and suffering and diminish the quality of life in this population. In addition, a moratorium as used here would significantly decrease patient access to pain medication and create an undue burden for patients, prescribers, dispensers and caregivers.

We are not aware of any data that has been presented, nor are we aware of any data that would warrant implementation of a moratorium or compassionate use program.

The IWG does not support a moratorium or compassionate use program for extended-release opioids and methadone. We firmly believe that if the class-wide REMS is properly designed and implemented, there will be a positive impact with a decrease in the risks contemplated in the class-wide REMS without creating an undue burden for patients, caregivers, and prescribers and dispensers.

8. PATIENT EDUCATION

Patients have stated that they have signed Prescriber-Patient Agreements but were not educated. How does the IWG propose ensuring that patients are educated when they sign these Agreements?

Signatures alone do not ensure patient education, and this is an area where the reach of industry is limited. While it is not possible to ensure that every patient is provided with the education that they should receive, there are steps that can be taken to maximize the likelihood that this does occur.

- Develop materials that clearly and consistently convey the risks contemplated in the class-wide REMS to patients who are prescribed extended-release opioids and methadone.
- Materials should be tested for literacy level and comprehension in a phased in program.
- Standardized information should be distributed and communicated at the time of prescribing to every patient, including:
  - PPA reviewed and signed by patient and prescriber, or designated staff.
  - Standardized patient educational materials would clearly communicate the dangers of misuse, abuse, diversion, overdose, and death associated with extended-release opioids and methadone. These materials would also contain pertinent information regarding safe storage and disposal.
  - Assess retention of knowledge and the potential need for re-education of patients through a well-developed survey instrument, in multiple delivery methods (telephone follow-up, available at the pharmacy, available on-line, at the prescriber's office).

In addition, there is an expectation that patient education continues with counseling at the pharmacy.

- Consistent safety messages should be reiterated at the pharmacy by the dispenser.

Appendix A

IWG PARTICIPATING COMPANIES

- Actavis
- Apotex
- Biodelivery Sciences International, Inc.
- Cephalon, Inc.
- Covidien Mallinckrodt
- Endo Pharmaceuticals
- Hisamitsu
- King Pharmaceuticals, Inc.
- KV Pharmaceutical
- Lavipharm Labs
- Mylan Technologies
- Neuromed Pharmaceuticals
- Ortho-McNeil-Janssen Pharmaceuticals, Inc.
- Purdue Pharma L.P.
- Ranbaxy Laboratories
- Roxane Laboratories
- Sandoz
- Teva Pharmaceutical Industries, Ltd.
- ThePharmaNetwork
- VistaPharm
- Watson Labs
- Xanodyne Pharmaceuticals, Inc.

Appendix B

Potential Metrics to be Measured in Class-wide REMS

Metric	Potential Data Source(s)
Patient Education 1. Did patients receive Medication Guide (MedGuide)? 2. Did patient receive Patient Medication Information Sheet? 3. Did they understand MedGuide? 4. Did they understand Patient Medication Information Sheet? 5. Do patients understand Patient-Prescriber Agreement? 6. From whom did the patients receive the Patient Medication Information Sheet and PPA? 7. Did anyone review the Patient Medication Information Sheet and PPA with the patient? 8. Have patients translated the information into appropriate use and best practices? 9. Why were you prescribed the extended-release opioid or methadone?	Patient Surveys National Health and Nutrition Examination Survey (NHANES)
Prescriber 1. Are the appropriate patients being selected to receive the medication? 2. Are medication errors occurring (e.g. inappropriate dose level)? 3. Has the comfort level among prescribers changed since REMS implementation? 4. Are prescribers being reimbursed for patient education	Prescriber Surveys Private Data: ▪ American Hospital Association and other industry organization
Dispenser 1. Has patient counseling increased for those patients receiving these medications? 2. Have number of prescriptions filled for these medications changed? 3. Have medication errors increased or decreased (e.g., splitting/crushing)?	Dispenser Surveys
Adverse Events (AEs) 1. Has there been a change in misuse,	Public Data: ▪ DAWN-ED

Metric	Potential Data Source(s)
abuse, diversion, and overdose deaths resulting from use of extended-release opioids or methadone? 2. Has there been an increase or decrease in street access to medications? 3. Has there been an increase or decrease in extended-release versus immediate-release prescription opioids? 4. Has there been an increase in the availability of counterfeit products? 5. Has there been increase or decrease in medication errors reported?	▪ National Survey on Drug Use and Health (NSDUH) ▪ Medical Expenditure Panel Survey (MEPS) ▪ National Hospital Discharge Survey (NHDS) ▪ National Poison Data System ▪ National Vital Statistics Report (specifically National Death Index) Private Data: ▪ RADARS System ▪ NAVIPPRO ▪ Pharmaceutical Proprietary Data ▪ SDI Vector One National Audit (VONA)
Access 1. Do various populations (e.g. rural, elderly, and other vulnerable populations) continue to have access to extended-release medications? 2. Have disparities in access emerged? 3. Has there been a change in coverage for extended-release opioids and methadone? a. Are extended-release opioids and methadone on an insurance company's formulary? b. Has there been an increase in purchasing pools? i. Are public and private organizations forming pools to purchase these products? 4. Are patients experiencing difficulty in paying for their prescriptions? 5. Are more patients obtaining products from foreign countries? 6. Is there an increase in the number of patients admitted to opioid treatment programs that are there primarily for pain treatment?	Public Data: ▪ Community Tracking Study (CTS), Physician and Household Surveys (conducted by Center for Studying Health System Change) ▪ Medical Expenditure Panel Survey (MEPS) ▪ National Ambulatory Medical Care Survey (NAMCS) ▪ National Healthcare Disparities Report (conducted by AHRQ) ▪ Patient Surveys Private Data: ▪ Claims Data ▪ Insurance Billing Data ▪ Prescription Drug Market Share ▪ RADARS OTP survey
Impact of REMS 1. What is the number of certified prescribers? 2. What is the number of participating	Private Data: ▪ IMS ▪ McKesson ▪ SDI Vector One National Audit

Metric	Potential Data Source(s)
pharmacies and pharmacists? 3. How many patients are prescribed extended-release opioids and methadone? 4. Has there been a change in the type of medications prescribed? a. Are long-acting prescription opioids being prescribed more or less than short-acting opioids? 5. Which patients are receiving extended-release opioids and methadone? a. Has there been a shift in demographics? b. Are patients with particular ailments (e.g. back pain, fibromyalgia, etc.) receiving extended-release opioids or methadone? 6. Has there been an increase or decrease in government regulation of drug prices? 7. Has there been an increase in awareness among the public regarding extended-release opioids and methadone?	(VONA) Public Data: ■ Medical Expenditure Panel Survey (MEPS) ■ Legislation ■ National Ambulatory Medical Care Survey (NAMCS) ■ DEA registration statistics
Quality of life 1. Do you feel stigmatized by the prescription? 2. Has your prescriber been suspicious of your use of the medication? 3. Have you had difficulties in obtaining your prescription at the pharmacy? 4. Has the patient's health outcome improved?	Patient Surveys Prescriber Surveys Dispenser Surveys
Costs 1. Has the cost of the medication increased since implementation of the REMS? 2. Are prescribers being reimbursed for education? 3. What is the cost of the REMS program? a. What are the administrative costs? b. What is the cost of the REMS program to the health care	Cost Analyses performed by Health Economists

Metric	Potential Data Source(s)
system? 4. Has a company's product pipeline been affected?	